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Original Article

Association of dynamic changes in ASPECTS perfusion scores derived from dual-time-point multi-post-labeling delay arterial spin labeling with 90-day functional outcome in acute ischemic stroke

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Abstract: Objective: To investigate whether dynamic changes in Alberta Stroke Program Early CT Score (ASPECTS) perfusion scores derived from dual-time-point multi-post-labeling delay arterial spin labeling (multi-PLD ASL) are associated with 90-day functional outcome in patients with acute ischemic stroke (AIS). Methods: This single-center retrospective study included 464 patients with anterior-circulation AIS who underwent multi-PLD ASL at baseline and approximately 1 week after onset. Cerebral blood flow (CBF)-ASPECTS, cerebral blood volume (CBV)-ASPECTS, arterial transit time (ATT)-ASPECTS, relative perfusion values, and infarct core volume (ICV) were compared between favorable (modified Rankin Scale [mRS] 0-2) and unfavorable (mRS 3-6) outcome groups. Correlation and receiver operating characteristic (ROC) analyses were performed. Results: The favorable outcome group showed greater improvements in CBF-ASPECTS, CBV-ASPECTS, ATT-ASPECTS, relative cerebral blood flow (rCBF), and relative cerebral blood volume (rCBV), together with a greater reduction in relative arterial transit time (rATT). Increased ICV was more pronounced in the unfavorable outcome group. Dynamic ASL indicators were significantly correlated with 90-day mRS scores. Single indicators showed moderate discriminative ability, whereas combined models performed better. The clinical-imaging model showed the highest area under the curve (AUC) of 0.846. Conclusion: Short-term changes on dual-time-point multi-PLD ASL were associated with 90-day functional outcome in AIS. Dynamic ASPECTS perfusion scores may serve as an interpretable imaging supplement for prognosis assessment, but should be combined with clinical information.

Keywords: Acute ischemic stroke, multi-post-labeling delay arterial spin labeling, ASPECTS perfusion score, cerebral perfusion, modified Rankin Scale, functional outcome

Introduction

Multi-post-labeling delay arterial spin labeling (multi-PLD ASL) is a cerebral perfusion assessment technique developed from conventional arterial spin labeling (ASL) imaging [1, 2]. Its imaging principle is to use arterial blood water protons as an endogenous tracer signal, allowing information related to cerebral tissue perfusion to be obtained without contrast administration [3]. Because of its noninvasive nature and good repeatability, multi-PLD ASL is suitable for perfusion assessment and dynamic follow-up in patients with cerebrovascular disease [4]. Unlike single-delay ASL, multi-PLD ASL uses multiple post-labeling delay time points in one acquisition, which more fully reflects the dynamic process by which labeled blood enters brain tissue [2]. This approach can reduce the influence of differences in arterial blood arrival time on perfusion measurements to some extent and improve the stability of perfusion quantification [5]. In addition to showing perfusion distribution, this technique provides data such as cerebral blood flow (CBF), cerebral blood volume (CBV), and arterial transit time (ATT), which help evaluate cerebral perfusion changes more comprehensively [5]. CBF describes the amount of blood entering local brain tissue per unit time and is an important mea-

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sure of the degree of cerebral perfusion. CBV mainly indicates changes in local blood volume and may partly reflect collateral circulation or perfusion compensation. ATT is used to determine whether the time for labeled blood to reach brain tissue is prolonged and may help identify delayed flow [2, 6]. In patients with acute ischemic stroke (AIS), the infarct lesion and surrounding tissue often show varying degrees of hypoperfusion, accompanied by delayed flow arrival [7]. Multi-PLD ASL can depict local hemodynamic status from several aspects and can help observe perfusion changes within and around the lesion. In addition, this method can support the identification of the spatial distribution of perfusion abnormalities, providing imaging reference information for evaluating disease evolution [8].

Acute ischemic stroke is a common cerebrovascular emergency, and patients often present with varying degrees of neurological impairment after onset [9, 10]. Population aging and common vascular risk factors, including hypertension, diabetes mellitus, and atrial fibrillation, continue to increase the clinical burden of AIS [11]. Although acute-phase diagnosis and treatment have been standardized to a considerable extent, some patients still experience poor recovery, manifested as limited limb movement, impaired speech function, or reduced ability to perform activities of daily living [12]. Early cerebral perfusion status after stroke is closely related to the progression of ischemic tissue, neurological recovery, and long-term functional outcome [13, 14]. Therefore, safe and repeatable imaging methods for observing cerebral perfusion changes may help clinicians further assess disease status and prognosis. Current studies on multi-PLD ASL or ASPECTS perfusion scores have often used findings from a single examination to explore their associations with functional outcomes in AIS. However, post-stroke cerebral perfusion is not fixed. Imaging information from a single time point reflects only the status at the time of examination and provides limited information on perfusion evolution from the early stage to the subacute stage after onset [15, 16]. Across different disease stages, the extent and severity of perfusion abnormalities may change with disease progression and treatment response [17]. Vascular recanalization, collateral compensation, treatment measures, and disease course may all affect blood flow status in the ischemic region and surrounding brain tissue [18]. Accordingly, the extent of perfusion abnormality may decrease, remain relatively stable, or further expand. Therefore, comparing ASL-based perfusion score changes at different time points can help describe cerebral perfusion evolution from a dynamic perspective. On this basis, the present study retrospectively collected dual-time-point multi-PLD ASL data from patients with AIS. The first magnetic resonance imaging (MRI) examination was performed in the early stage after onset, and follow-up MRI was performed approximately 1 week later. ASPECTS regional scoring was applied to CBF, CBV, and ATT maps, and changes in CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS were calculated. Functional status was assessed using the 90-day modified Rankin Scale (mRS). This score was then used to examine the relationship between perfusion score changes and clinical outcome. Rather than evaluating only a single early perfusion status, this study focused on changes in perfusion scores during short-term follow-up, aiming to provide additional information on perfusion recovery and prognosis assessment in patients with AIS.

Patients and methods

Patients

The study was conducted at Suzhou Wuzhong People's Hospital from January 2021 to January 2026. All patients received treatment according to the then-current clinical guidelines for AIS. Treatment measures included medical therapy, intravenous thrombolysis, endovascular treatment, and bridging therapy. The treatment plan was determined by the attending physician after comprehensive consideration of the time window from onset, imaging features, vascular assessment results, and the overall condition of each patient. This study did not alter the original diagnostic or therapeutic workflow and retrospectively analyzed existing clinical and imaging data. The retrospective study protocol was approved by the Ethics Committee of Suzhou Wuzhong People's Hospital (Approval No. 2024KY03).

Eligible patients had undergone MRI in the early stage after onset and again at about 1

week after onset, with multi-PLD ASL included in both examinations. The 90-day mRS score was used to define functional outcome. Patients with mRS scores of 0-2 were assigned to the favorable outcome group, whereas those with scores of 3-6 were assigned to the unfavorable outcome group [19]. The mRS is a widely used measure of post-stroke functional status [20]. In this study, it was used to describe short- to medium-term recovery.

The study design referred to relevant content from the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2023 and the American Heart Association/American Stroke Association (AHA/ASA) guidelines for early management of AIS [10, 21].

Inclusion criteria were as follows: (1) AIS confirmed by clinical symptoms and MRI findings; (2) age ≥ 18 years; (3) completion of the first MRI examination in the early stage after onset; (4) completion of a second MRI examination at approximately 1 week after onset; (5) inclusion of multi-PLD ASL sequences in both MRI examinations, with CBF, CBV, and ATT maps of sufficient quality for analysis; (6) infarct lesions located in the anterior circulation territory and suitable for ASPECTS regional scoring; and (7) complete clinical records, imaging data, and 90-day mRS functional outcome follow-up after onset.

Exclusion criteria were as follows: (1) poor MRI image quality or obvious motion artifacts that prevented accurate ASL post-processing or ASPECTS perfusion scoring [22]; (2) infratentorial or posterior circulation infarction, extensive bilateral cerebral infarction, or lesion distribution unsuitable for ASPECTS regional evaluation. ASPECTS is mainly used for semi-quantitative evaluation of acute ischemic changes in the middle cerebral artery territory [23]; (3) hemorrhagic transformation or other intracranial hemorrhagic lesions suggested by imaging; (4) obvious encephalomalacia, cerebral atrophy, or other imaging abnormalities from previous stroke that affected the assessment of the current infarct lesion and perfusion abnormality extent [24]; (5) other intracranial diseases that might affect imaging evaluation, such as brain tumors, cerebrovascular malformations, head trauma, and intracranial infection; (6) MRI examinations outside the prespecified time windows or absence of multi-PLD ASL images at either time point; and (7) incomplete clinical data, absence of 90-day mRS data after onset.

During the study period, 621 patients with AIS were initially screened. After application of the inclusion and exclusion criteria, 464 patients were included in the final statistical analysis. According to the 90-day mRS score after onset, 261 patients had favorable outcomes and 203 had unfavorable outcomes. The detailed screening process is shown in **Figure 1**.

Study methods

Clinical information and imaging examination data were retrospectively collected and analyzed. General information, medical history, neurological function score at admission, treatment modality, and 90-day functional follow-up results were collected through the hospital electronic medical record system. MRI data from both time points were retrieved from the picture archiving and communication system (PACS). All patients underwent routine MRI combined with multi-PLD ASL scanning. Routine MRI mainly included diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) mapping, T2-weighted imaging (T2WI), T2-fluid attenuated inversion recovery (T2-FLAIR), and magnetic resonance angiography (MRA), which were used to evaluate acute ischemic lesions and intracranial vascular status [10]. Multi-PLD ASL was used to obtain perfusion parameter maps including CBF, CBV, and ATT. Based on the perfusion maps from the two multi-PLD ASL examinations, CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS scores were recorded at the early stage after onset and at 1 week after onset, and score changes between the two examinations were calculated. By comparing changes in perfusion scores, dynamic changes in the extent of cerebral perfusion abnormalities from the early stage after onset to 1 week after onset were evaluated, and their associations with 90-day functional outcome were further analyzed.

MRI examination methods: All MRI data were obtained from clinical examinations completed during hospitalization. MRI assessment time points were set at the initial examination in the early stage after onset and at the follow-up examination approximately 1 week after onset. The examinations included routine MRI sequences and multi-PLD ASL sequences. Images

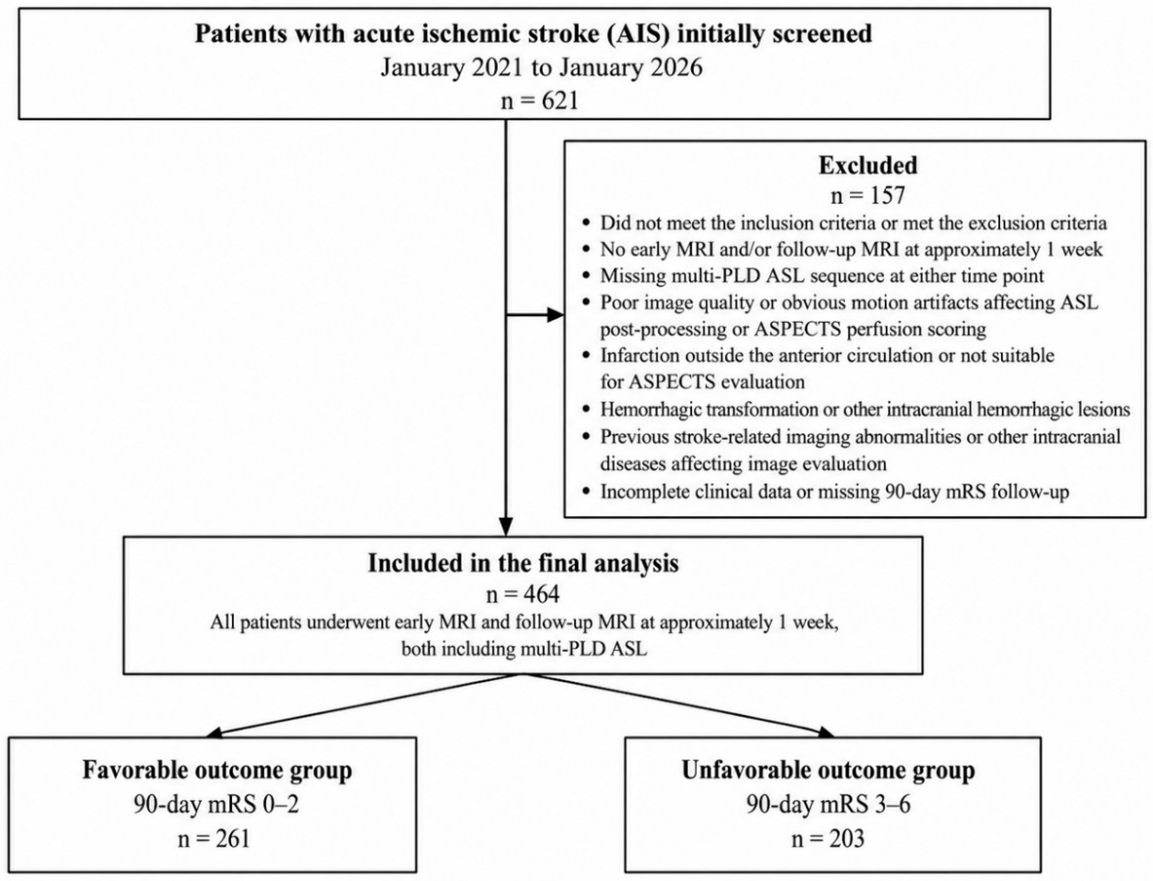

Figure 1. Flowchart of patient selection.

were acquired on a GE Discovery 750W 3.0-T MRI scanner with a 24-channel head and neck coil. The routine MRI protocol included DWI, ADC mapping, T2WI, T2-FLAIR, and MRA [26]. The multi-PLD ASL sequence was performed using the following parameters: repetition time, 5,978 ms; echo time, 11.5 ms; field of view, 220 × 220 mm^2; in-plane resolution, 4.67 × 4.67 mm^2; slice thickness, 4.5 mm; number of slices, 106; number of excitations, 1; post-labeling delays, 1,000/1,220/1,480/1,780/2,100/2,630/3,320 ms; and acquisition time, 4 min 2 s. The multi-PLD ASL sequence generated CBF, CBV, and ATT maps. Images and scan-related information were obtained from the institutional picture archiving and communication system (PACS).

Imaging scoring methods: The previously stored multi-PLD ASL images were retrospectively analyzed. Raw ASL data were post-processed using CereFlow software (Anmage, Beijing, China). Post-processing mainly included motion correction, noise correction, and subtraction between labeled and control images. CBF, CBV, and ATT parameter maps were then generated based on the perfusion model. During image review, each parameter map was compared with the corresponding DWI, ADC, and routine MRI images to reduce errors in identifying the infarct extent and perfusion abnormality area.

Infarct core volume (ICV) and perfusion parameters in regions of interest were measured using Astroke 1.0 software. The software first identified the infarct core according to regions with ADC < 620 × 10^-6 mm^2/s, followed by correction based on radiologist interpretation. CBF, CBV, and ATT values were then extracted from the infarct side and corresponding contralateral regions, and relative perfusion parameters were calculated. Relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and relative arterial transit time (rATT) were defined as the ratios of CBF, CBV, and ATT

on the infarct side to the corresponding contralateral parameters, respectively. CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS were obtained from the corresponding parameter maps. Scoring regions included the caudate nucleus, lentiform nucleus, internal capsule, insula, and the M1-M6 regions of the middle cerebral artery territory. After image standardization, corresponding ASPECTS regions on the affected and unaffected sides were compared, and the perfusion asymmetry index was calculated as (affected side - unaffected side)/(affected side + unaffected side) × 2. For CBF and CBV, perfusion reduction was identified when the affected side was lower than the unaffected side and exceeded the prespecified threshold. For ATT, delayed flow arrival was identified when the affected side was higher than the unaffected side and exceeded the prespecified threshold. In this study, an absolute asymmetry index > 0.2 was used as the threshold for regional abnormality. This threshold represented an interhemispheric relative difference of approximately 20% and was prespecified to reduce false-positive regional scoring caused by minor physiologic asymmetry or image noise. ASPECTS perfusion scoring was independently performed by two experienced radiologists who were blinded to the 90-day mRS outcome. Inter-reader reliability was assessed using the two readers' initial independent scores before consensus. Intraclass correlation coefficients (ICCs) were calculated for total ASPECTS perfusion scores, and weighted kappa values were calculated for regional abnormality classification. When discrepancies occurred, consensus was reached through discussion, and the consensus scores were used for the final statistical analysis.

Clinical data and outcome indicators: This study retrospectively collected previous clinical information from the hospital electronic medical record system. Extracted data included age, sex, time from onset to first MRI, and other basic information; medical history and related risk factors, including hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking, and alcohol consumption; and treatment information, including conventional medical therapy, intravenous thrombolysis, endovascular treatment, and bridging therapy. Neurological deficit severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. The NIHSS can quantify neurological impairment in patients with acute stroke and assist in judging the severity of disease at admission [27, 28].

Functional outcome was evaluated using the 90-day modified Rankin Scale (mRS) score after onset. The mRS is mainly used to evaluate disability and dependence in activities of daily living after stroke and is a commonly used functional outcome measure in stroke clinical research and efficacy evaluation [29]. Patients were divided into a favorable outcome group and an unfavorable outcome group according to the 90-day mRS score. An mRS score of 0-2 was defined as a favorable outcome, indicating no obvious disability or only mild disability and basic independence in daily life. An mRS score of 3-6 was defined as an unfavorable outcome, indicating poor functional recovery after onset, including moderate to severe disability, obvious dependence on others for care, or death [30]. This grouping method is widely used in prognostic studies of AIS and can intuitively reflect 90-day functional recovery.

The main outcomes of this study included the 90-day mRS score after onset and the functional outcome category defined accordingly. The main observation indicators were changes in CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS from the early stage after onset to 1 week after onset, namely ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS, and their associations with 90-day mRS score were analyzed. Secondary observation indicators included general clinical data, baseline NIHSS score, treatment modality, ICV, and differences in dual-time-point ASL perfusion scores between the two groups.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 27.0. Continuous variables were tested for normality and compared using the independent-samples t test or Mann-Whitney U test, as appropriate. Categorical variables were analyzed with the Pearson chi-square test or Fisher's exact test. Changes in ASL indicators were calculated as follow-up values minus baseline values. Paired comparisons used the paired t-test or Wilcoxon signed-rank test. Spearman correlation analysis was

Table 1. Comparison of baseline clinical characteristics and treatment details between the two groups

Variable	Overall (n=464)	Favorable outcome group mRS 0-2 (n=261)	Unfavorable outcome group mRS 3-6 (n=203)	Statistic	*P* value
Age (years)	69.0 (54.3, 77.0)	66.0 (52.0, 74.0)	73.0 (59.0, 80.0)	Z=-5.778	< 0.001
Sex				χ^2=0.355	0.551
Male	295 (63.6)	169 (64.8)	126 (62.1)		
Female	169 (36.4)	92 (35.2)	77 (37.9)		
Time from onset to first MRI (h)	4.3 (3.4, 5.7)	4.0 (3.2, 5.3)	4.7 (3.7, 6.2)	Z=4.951	< 0.001
Time from onset to follow-up MRI (d)	8.0 (6.0, 9.0)	8.0 (7.0, 9.0)	7.0 (6.0, 9.0)	Z=-1.255	0.210
Hypertension	330 (71.1)	182 (69.7)	148 (72.9)	χ^2=0.560	0.454
Diabetes mellitus	142 (30.6)	71 (27.2)	71 (35.0)	χ^2=3.248	0.072
Hyperlipidemia	212 (45.7)	128 (49.0)	84 (41.4)	χ^2=2.702	0.100
Atrial fibrillation	123 (26.5)	61 (23.4)	62 (30.5)	χ^2=3.013	0.083
Smoking history	173 (37.3)	101 (38.7)	72 (35.5)	χ^2=0.509	0.475
Drinking history	126 (27.2)	74 (28.4)	52 (25.6)	χ^2=0.432	0.511
Baseline NIHSS score	8.0 (5.3, 12.0)	6.0 (4.0, 9.0)	11.0 (8.0, 14.0)	Z=6.721	< 0.001
Intravenous thrombolysis	276 (59.5)	161 (61.7)	115 (56.7)	χ^2=1.201	0.273
Endovascular treatment	152 (32.8)	78 (29.9)	74 (36.5)	χ^2=2.236	0.135
Bridging therapy	91 (19.6)	47 (18.0)	44 (21.7)	χ^2=0.974	0.324
Conventional medical therapy alone	127 (27.4)	69 (26.4)	58 (28.6)	χ^2=0.262	0.609

Note: Continuous variables are shown as mean ± standard deviation or median (interquartile range), depending on distribution. Categorical variables are summarized as number (percentage). Intravenous thrombolysis, endovascular treatment, and bridging therapy were recorded according to whether the corresponding treatment was performed. Conventional medical therapy alone refers to patients who did not receive reperfusion therapy.

used to assess the association between ASL changes and 90-day mRS scores. ROC analysis was performed to evaluate the predictive value of dynamic ASL indicators for unfavorable outcomes. Combined models were built using binary logistic regression, and the predicted probabilities were used for ROC analysis. The models included dynamic imaging changes, quantitative perfusion changes, and ASPECTS score changes. Multivariable logistic regression was used to identify factors independently associated with unfavorable 90-day outcome. Inter-reader reliability was assessed using ICCs for total ASPECTS perfusion scores and weighted kappa values for regional abnormality classification. Subgroup analyses were performed to assess the stability of the clinical-imaging model across prespecified clinical subgroups.

Results

Baseline clinical characteristics of patients with different outcomes

As shown in **Table 1**, the median age of patients in the unfavorable outcome group was 73.0 (59.0, 80.0) years, significantly higher than that in the favorable outcome group [66.0 (52.0, 74.0) years] (P < 0.001). The time from onset to first MRI was 4.7 (3.7, 6.2) h in the unfavorable outcome group, which was longer than that in the favorable outcome group [4.0 (3.2, 5.3) h] (P < 0.001). In addition, the baseline NIHSS score was 11.0 (8.0, 14.0) in the unfavorable outcome group, higher than 6.0 (4.0, 9.0) in the favorable outcome group (P < 0.001). This indicated more severe neurological deficits in the unfavorable outcome group in the early stage after onset. No significant differences were observed between the two groups in sex, time from onset to follow-up MRI, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking history, drinking history, or acute-phase treatment modality (all P > 0.05). Overall, patients with unfavorable outcomes were mainly characterized by older age, later first MRI examination, and higher baseline NIHSS scores.

Baseline imaging perfusion characteristics of patients with different outcomes

Inter-reader reliability for ASPECTS perfusion scoring was acceptable to excellent. The ICCs

Table 2. Comparison of baseline imaging and perfusion indicators in patients with different outcomes

Variable	Overall (n=464)	Favorable outcome group mRS 0-2 (n=261)	Unfavorable outcome group mRS 3-6 (n=203)	Statistic	*P* value
Baseline CBF-ASPECTS	7.0 (7.0, 8.0)	8.0 (7.0, 8.0)	7.0 (7.0, 8.0)	Z=-6.088	< 0.001
Baseline CBV-ASPECTS	7.0 (7.0, 8.0)	8.0 (8.0, 9.0)	7.0 (7.0, 8.0)	Z=-5.785	< 0.001
Baseline ATT-ASPECTS	7.0 (6.0, 8.0)	7.0 (7.0, 8.0)	6.0 (6.0, 7.0)	Z=-8.250	< 0.001
Baseline rCBF	0.7 (0.6, 0.8)	0.8 (0.6, 0.8)	0.7 (0.6, 0.8)	Z=-5.623	< 0.001
Baseline rCBV	0.9 (0.8, 1.0)	1.0 (0.9, 1.1)	0.9 (0.8, 1.0)	Z=-3.986	< 0.001
Baseline rATT	1.4 (1.3, 1.6)	1.4 (1.2, 1.5)	1.5 (1.4, 1.6)	Z=7.023	< 0.001
ICV (mL)	12.4 (9.0, 16.6)	9.8 (7.8, 12.8)	15.3 (12.6, 20.5)	Z=7.602	< 0.001

Note: Continuous variables are summarized as median (interquartile range). Non-normally distributed variables were analyzed using the Mann-Whitney U test. *P* values refer to comparisons between the favorable and unfavorable outcome groups.

for total CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS scores were 0.760, 0.753, and 0.710 at baseline, and 0.903, 0.887, and 0.876 at 1-week follow-up, respectively. Weighted kappa values for regional abnormality classification ranged from 0.801 to 0.846, indicating good inter-reader agreement. The detailed results are shown in Supplementary Table 2.

Table 2 shows that baseline CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS scores were lower in the unfavorable outcome group than in the favorable outcome group (all P < 0.001). In the unfavorable outcome group, baseline CBF-ASPECTS was 7.0 (7.0, 8.0), CBV-ASPECTS was 7.0 (7.0, 8.0), and ATT-ASPECTS was 6.0 (6.0, 7.0), all lower than those in the favorable outcome group. Quantitative perfusion parameter comparisons showed that baseline rCBF and rCBV were lower in the unfavorable outcome group, whereas rATT was higher than in the favorable outcome group (all P < 0.001). In addition, ICV in the unfavorable outcome group was 15.3 (12.6, 20.5) mL, higher than 9.8 (7.8, 12.8) mL in the favorable outcome group (P < 0.001). These results suggest that patients with unfavorable 90-day outcomes already had more obvious hypoperfusion, reduced blood volume, and delayed flow arrival at baseline, accompanied by larger infarct core volume.

Representative dual-time-point imaging findings are shown in **Figure 2**. Compared to the favorable outcome case, the unfavorable outcome case showed more persistent perfusion impairment and arterial transit delay on follow-up ASL images.

Short-term dynamic changes in ASL perfusion scores and parameters

As shown in **Table 3**, CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS scores increased at 1 week after onset compared with baseline (all P < 0.001). Specifically, CBF-ASPECTS increased from 7.0 (7.0, 8.0) to 8.0 (7.0, 9.0), CBV-ASPECTS increased from 7.0 (7.0, 8.0) to 9.0 (7.0, 10.0), and ATT-ASPECTS increased from 7.0 (6.0, 8.0) to 8.0 (6.0, 9.0). Quantitative perfusion parameters showed similar changes: rCBF and rCBV increased compared with baseline, while rATT decreased (all P < 0.001). Meanwhile, ICV increased from 12.4 (9.0, 16.6) mL to 13.1 (9.5, 18.4) mL (P < 0.001). These results suggest that overall perfusion status at 1 week after onset improved compared with baseline, mainly reflected by increased perfusion-related ASPECTS scores, improved relative perfusion values, and shortened arterial transit time. However, ICV still increased, indicating that infarct core evolution continued in some patients in the short term.

Short-term perfusion change characteristics in patients with different outcomes

Table 4 further compares dynamic changes in ASL-related indicators within 1 week after onset between patients with different outcomes. Compared to the unfavorable outcome group, the favorable outcome group showed more obvious improvements in CBF-ASPECTS, CBV-ASPECTS, and ATT-ASPECTS. The median values of all three ΔASPECTS indicators were 1.0 in the favorable outcome group and 0.0 in the unfavorable outcome group (all P < 0.001).

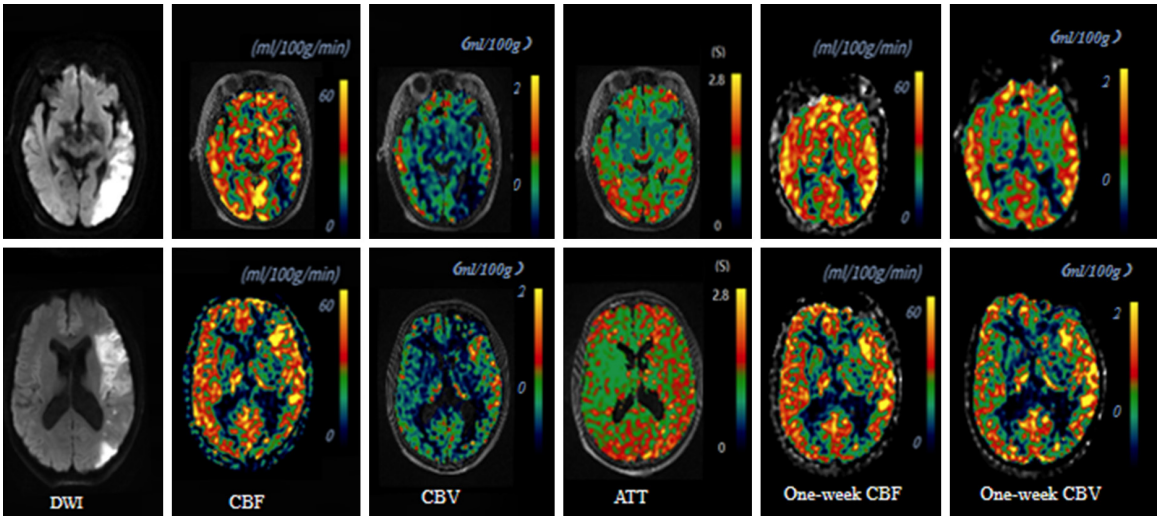

Figure 2. Representative dual-time-point multi-PLD ASL imaging findings in patients with different outcomes. Note: Representative images are provided for patients with favorable and unfavorable 90-day outcomes. The upper row presents a case from the favorable outcome group, and the lower row presents a case from the unfavorable outcome group. Baseline DWI and ASL-derived CBF, CBV, and ATT maps are shown, together with follow-up CBF and ATT maps obtained about 1 week after onset. The favorable outcome case demonstrates partial perfusion recovery and attenuation of arterial transit delay at follow-up. The unfavorable outcome case shows persistent perfusion impairment and delayed arterial transit.

Table 3. Changes in ASL perfusion scores and values from baseline to 1 week after onset in the overall cohort (n=464)

Variable	Baseline	At 1 week after onset	Change Δ	Statistic	*P* value
CBF-ASPECTS	7.0 (7.0, 8.0)	8.0 (7.0, 9.0)	1.0 (0.0, 1.0)	Z=8.034	< 0.001
CBV-ASPECTS	7.0 (7.0, 8.0)	9.0 (7.0, 10.0)	1.0 (1.0, 2.0)	Z=7.325	< 0.001
ATT-ASPECTS	7.0 (6.0, 8.0)	8.0 (6.0, 9.0)	1.0 (1.0, 2.0)	Z=6.675	< 0.001
rCBF	0.7 (0.6, 0.8)	0.8 (0.7, 1.0)	0.1 (0.0, 0.2)	Z=7.011	< 0.001
rCBV	0.9 (0.8, 1.0)	1.0 (0.9, 1.1)	0.05 (0.0, 0.10)	Z=7.605	< 0.001
rATT	1.4 (1.3, 1.6)	1.3 (1.2, 1.5)	-0.1 (-0.3, 0.0)	Z=-8.210	< 0.001
ICV (mL)	12.4 (9.0, 16.6)	13.1 (9.5, 18.4)	1.0 (-0.7, 2.1)	Z=7.449	< 0.001

Note: Baseline values, 1-week values, and Δ values are presented as median (interquartile range). Δ was calculated as the value at 1 week after onset minus the baseline value. *P* values refer to paired comparisons within the same patients. The Wilcoxon signed-rank test was applied, and the statistic is reported as Z.

Table 4. Comparison of changes in ASL perfusion scores and values in patients with different outcomes

Variable	Favorable outcome group mRS 0-2 (n=261)	Unfavorable outcome group mRS 3-6 (n=203)	Statistic	*P* value
ΔCBF-ASPECTS	1.0 (0.0, 1.0)	0.0 (-1.0, 1.0)	Z=-7.305	< 0.001
ΔCBV-ASPECTS	1.0 (0.0, 1.0)	0.0 (-1.0, 1.0)	Z=-7.272	< 0.001
ΔATT-ASPECTS	1.0 (0.0, 1.0)	0.0 (-1.0, 1.0)	Z=-6.295	< 0.001
ΔrCBF	0.1 (0.0, 0.2)	0.1 (-0.02, 0.1)	Z=-6.757	< 0.001
ΔrCBV	0.07 (0.02, 0.13)	0.03 (-0.03, 0.07)	Z=-6.082	< 0.001
ΔrATT	-0.1 (-0.2, -0.1)	-0.04 (-0.1, 0.1)	Z=4.831	< 0.001
ΔICV (mL)	0.5 (-0.4, 1.7)	1.6 (0.6, 2.6)	Z=5.711	< 0.001

Note: Values are expressed as median (interquartile range). Δ indicates the 1-week value minus the baseline value. The Mann-Whitney U test was used for comparisons of changes between groups, and the statistic is shown as Z.

Table 5. Correlation analysis between changes in ASL perfusion scores or values and 90-day mRS score

Variable	r_s value	*P* value
ΔCBF-ASPECTS vs 90-day mRS	-0.427	< 0.001
ΔCBV-ASPECTS vs 90-day mRS	-0.531	< 0.001
ΔATT-ASPECTS vs 90-day mRS	-0.438	< 0.001
ΔrCBF vs 90-day mRS	-0.408	< 0.001
ΔrCBV vs 90-day mRS	-0.562	< 0.001
ΔrATT vs 90-day mRS	0.470	< 0.001
ΔICV vs 90-day mRS	0.482	< 0.001

Note: Δ was calculated as the value at 1 week after onset minus the baseline value. Spearman rank correlation analysis was performed between each dynamic indicator and the 90-day mRS score. r_s denotes the Spearman correlation coefficient, and *P* values are two-sided. Higher mRS scores indicate poorer functional outcome. A negative r_s indicates that a larger increase is related to a lower 90-day mRS score; a positive r_s indicates that a larger increase is related to a higher 90-day mRS score.

Quantitative perfusion parameters showed that ΔrCBF was 0.1 (0.0, 0.2) in the favorable outcome group and 0.1 (-0.02, 0.1) in the unfavorable outcome group. Although the median ΔrCBF was the same in the two groups, the interquartile ranges differed, and the distribution difference remained significant. ΔrCBV was 0.07 (0.02, 0.13) in the favorable outcome group, higher than 0.03 (-0.03, 0.07) in the unfavorable outcome group (P < 0.001). ΔrATT was -0.1 (-0.2, -0.1) in the favorable outcome group and -0.04 (-0.1, 0.1) in the unfavorable outcome group, suggesting a more marked shortening of arterial transit time in patients with favorable outcome. Conversely, ΔICV was 1.6 (0.6, 2.6) mL in the unfavorable outcome group, higher than 0.5 (-0.4, 1.7) mL in the favorable outcome group, indicating more pronounced short-term enlargement of infarct core volume. These results indicate that patients with favorable 90-day outcomes not only had relatively better baseline perfusion status but also showed more obvious perfusion recovery within 1 week after onset. In contrast, patients with unfavorable outcomes mainly showed insufficient perfusion improvement, limited improvement in arterial transit time, and more obvious increase in infarct core volume.

Correlations between ASL perfusion change indicators and 90-day functional outcome

The correlations between changes in ASL perfusion scores or parameters and 90-day mRS score are shown in **Table 5**. The results showed that ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS were all negatively correlated with 90-day mRS score, with correlation coefficients of -0.427, -0.531, and -0.438, respectively (all P < 0.001). Among them, ΔCBV-ASPECTS showed a relatively stronger correlation, suggesting that greater improvement in the extent of perfusion abnormality within 1 week after onset was generally associated with lower 90-day mRS scores. For quantitative perfusion values, ΔrCBF and ΔrCBV were also negatively correlated with 90-day mRS score, with r_s values of -0.408 and -0.562, respectively (both P < 0.001), indicating that patients with larger increases in relative cerebral blood flow and relative cerebral blood volume had relatively better long-term functional outcomes. In contrast, ΔrATT was positively correlated with 90-day mRS score (r_s=0.470, P < 0.001), suggesting that patients with insufficient reduction or further prolongation of relative arterial transit time may have higher 90-day mRS scores. In addition, ΔICV was positively correlated with 90-day mRS score (r_s=0.482, P < 0.001), indicating that greater infarct core volume enlargement was associated with poorer long-term functional prognosis. These results indicate that the degree of ASL perfusion improvement, changes in arterial transit time, and infarct core volume evolution within 1 week after onset were all correlated with 90-day functional outcome. Among these indicators, ΔCBV-ASPECTS and ΔrCBV showed relatively stronger correlations with 90-day mRS score.

Prognostic discriminative value of key ASL perfusion change indicators

Table 6 shows that ASL perfusion change indicators within 1 week after onset had discriminative value for unfavorable 90-day outcomes. Among individual indicators, the AUCs of ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS were 0.689, 0.682, and 0.692, respectively, and all differences were statistically significant (all P < 0.001). The optimal cutoff values for all three indicators were ≤ 0.5. The corresponding sensitivity ranged from 64.0% to 66.0%, and specificity ranged from 63.2% to 67.4%. **Figure 3** shows that the ROC curves of all single indicators were above the reference line. The curves showed similar trends across different indicators.

Quantitative perfusion parameters also had certain discriminative ability. The AUCs of

Table 6. ROC analysis of ASL perfusion change indicators and combined models for unfavorable 90-day outcome

Indicator/model	AUC	95% CI	Optimal cutoff	Sensitivity (%)	Specificity (%)	*P* value
ΔCBF-ASPECTS	0.689	0.640-0.738	≤ 0.5	64.0	66.7	< 0.001
ΔCBV-ASPECTS	0.682	0.633-0.731	≤ 0.5	66.0	63.2	< 0.001
ΔATT-ASPECTS	0.692	0.643-0.739	≤ 0.5	64.0	67.4	< 0.001
ΔrCBF	0.683	0.634-0.731	≤ 0.107	67.0	64.4	< 0.001
ΔrCBV	0.684	0.636-0.732	≤ 0.0485	64.5	64.8	< 0.001
ΔrATT	0.683	0.634-0.732	≥ -0.0855	64.5	65.9	< 0.001
ΔICV (mL)	0.685	0.637-0.733	≥ 1.115	65.0	64.8	< 0.001
Model 1: Dynamic imaging combined model	0.786	0.746-0.827	≥ 0.430	74.4	69.0	< 0.001
Model 2: Quantitative perfusion parameter model	0.748	0.705-0.792	≥ 0.452	66.5	70.5	< 0.001
Model 3: ASPECTS dynamic score model	0.798	0.757-0.838	≥ 0.341	75.4	69.3	< 0.001
Model 4: Clinical-imaging model	0.846	0.812-0.881	≥0.515	69.5	83.5	< 0.001

Note: For each combined model, prediction probabilities were generated by binary logistic regression and then entered into ROC analysis. Model 1, the dynamic imaging combined model, included ΔCBV-ASPECTS, ΔrCBV, ΔrATT, and ΔICV, representing perfusion extent, quantitative perfusion delay, and infarct core evolution. Model 2, the quantitative perfusion parameter model, included ΔrCBF, ΔrCBV, and ΔrATT. Model 3, the ASPECTS dynamic score model, included ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS. Model 4, the clinical-imaging model, included age, time from onset to first MRI, baseline NIHSS score, ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS. Lower ΔCBF-ASPECTS, ΔCBV-ASPECTS, ΔATT-ASPECTS, ΔrCBF, and ΔrCBV values indicate greater risk of unfavorable outcome; higher ΔrATT, ΔICV, and model-predicted probabilities indicate greater risk. The optimal cutoff was selected using the Youden index. For ΔASPECTS indicators, a cutoff of 0.5 separated Δ ≤ 0 from Δ ≥ 1.

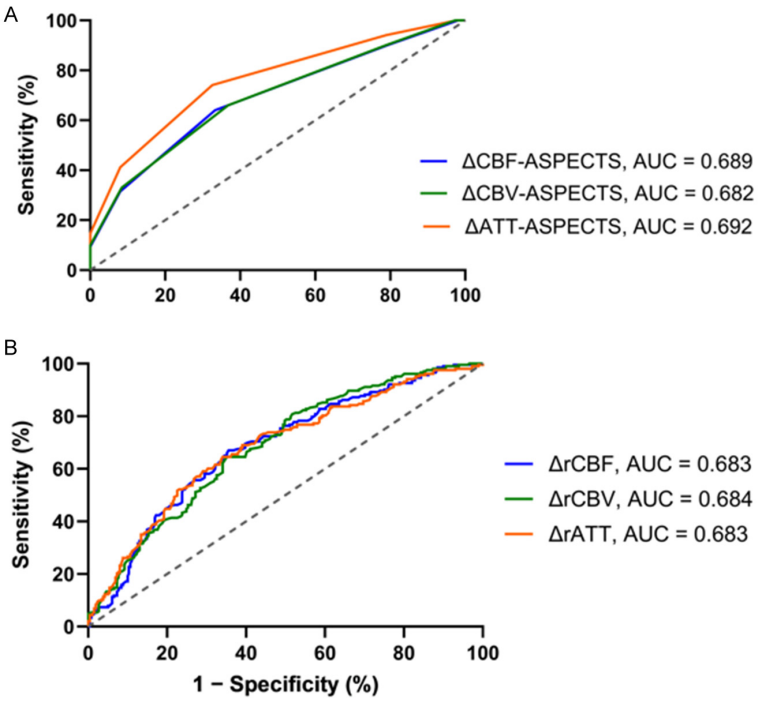

Figure 3. Receiver operating characteristic curves for ASL perfusion change indicators in predicting unfavorable 90-day outcomes. A. ASPECTS-based perfusion change indicators, including ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS. B. Quantitative perfusion value changes, including ΔrCBF, ΔrCBV, and ΔrATT.

ΔrCBF, ΔrCBV, and ΔrATT were 0.683, 0.684, and 0.683, respectively, all with P < 0.001. The AUC of ΔICV was 0.685, with an optimal cutoff value of ≥ 1.115 mL. Its sensitivity was 65.0%, and specificity was 64.8%. These results indicate that the magnitude of perfusion improvement, changes in arterial transit time, and infarct core volume progression can all reflect the risk of long-term functional outcome.

The discriminative performance of combined models was further improved. Model 1 was the dynamic imaging combined model, with an AUC of 0.786, sensitivity of 74.4%, and specificity of 69.0%. Model 2 was the quantitative perfusion parameter model, with an AUC of 0.748, sensitivity of 66.5%, and specificity of 70.5%. Model 3 was the ASPECTS dynamic score model and had an AUC of 0.798. Its optimal cutoff value was 0.341, sensitivity was 75.4%, and specificity was 69.3%. Model 4 was the clinical-imaging model and showed the best discriminative performance, with an AUC of 0.846, an optimal cutoff value of 0.515, sensitivity of 69.5%, and

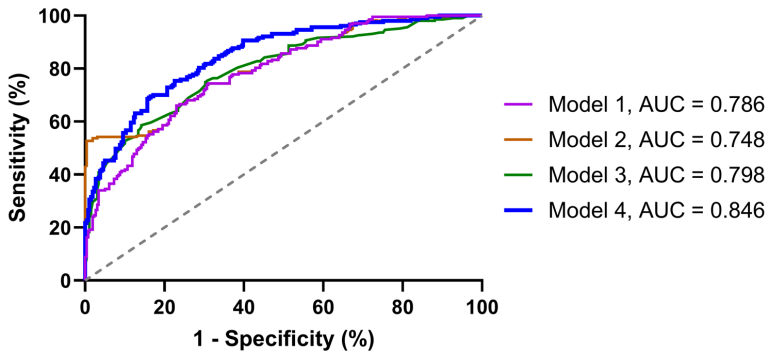

Figure 4. ROC curves for the combined ASL perfusion change models in predicting unfavorable 90-day outcome.

specificity of 83.5%. Subgroup analysis showed that the clinical-imaging model generally maintained discriminative performance across different patient subgroups, although the estimates varied slightly between subgroups, as shown in Supplementary Table 1. **Figure 4** shows that the ROC curves of the four combined models were generally above the reference line. The curve of Model 4 was closer to the upper-left corner. Its discriminative performance was the highest among the four models.

Overall, dual-time-point ASL perfusion changes can provide useful information for 90-day prognosis assessment. Compared to individual indicators, combined models showed better discriminative ability. Among them, the clinical-imaging model performed best, suggesting that integration of clinical information and dynamic ASL perfusion changes may provide a more comprehensive basis for assessing long-term functional prognosis in patients with AIS.

Multivariable logistic regression analysis

As shown in **Table 7**, multivariable logistic regression was performed with unfavorable 90-day functional outcome as the dependent variable. Age, time from onset to first MRI, and baseline NIHSS score were associated with an increased risk of unfavorable outcome. Older age was associated with higher odds of unfavorable outcome (OR=1.030, 95% CI: 1.012-1.049, P=0.001). A longer time from onset to first MRI was also related to increased risk (OR=1.248, 95% CI: 1.065-1.464, P=0.006). Higher baseline NIHSS score showed a similar association (OR=1.195, 95% CI: 1.118-1.278, P < 0.001). In contrast, higher ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS were independently associated with lower odds of an unfavorable 90-day functional outcome, with ORs of 0.638, 0.599, and 0.668, respectively. These findings indicate that dual-time-point ASL perfusion changes remained related to 90-day functional prognosis after adjustment for clinical factors. Greater improvement in perfusion abnormality was associated with better functional outcome.

Discussion

This study used dual-time-point multi-PLD ASL to observe perfusion changes from the early stage after onset to approximately 1 week after onset in patients with AIS. The results showed that patients with unfavorable outcome already had a heavier clinical and imaging burden at baseline, mainly reflected by older age, higher NIHSS scores, a wider hypoperfusion extent, more obvious ATT prolongation, and larger ICV. At follow-up 1 week after onset, overall perfusion indicators improved, but the magnitude of recovery differed across patients. Patients with favorable outcomes showed more pronounced increases in ASPECTS perfusion scores and a more sufficient reduction in rATT. In contrast, patients with unfavorable outcomes mainly showed insufficient perfusion recovery accompanied by increased ICV. In multivariable analysis, greater improvements in ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS remained associated with lower odds of unfavorable 90-day outcome after adjustment for age, time from onset to first MRI, and baseline NIHSS score. These findings suggest that a single baseline image primarily reflects ischemia and perfusion impairment at the time of examination, whereas dual-time-point observation can further show the short-term direction of lesion evolution. This represents an important value of the present study compared to single-time-point assessment.

From a pathophysiologic perspective, functional recovery after stroke does not depend only

Table 7. Multivariable logistic regression analysis of factors independently associated with unfavorable 90-day functional outcome

Variable	β	SE	Adjusted OR	95% CI	*P* value
Age, years	0.030	0.009	1.030	1.012-1.049	0.001
Time from onset to first MRI, h	0.222	0.081	1.248	1.065-1.464	0.006
Baseline NIHSS score	0.176	0.034	1.195	1.118-1.278	< 0.001
ΔCBF-ASPECTS	-0.449	0.124	0.638	0.501-0.814	< 0.001
ΔCBV-ASPECTS	-0.513	0.125	0.599	0.469-0.764	< 0.001
ΔATT-ASPECTS	-0.404	0.120	0.668	0.528-0.845	< 0.001

Note: β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; ATT, arterial transit time.

on the initial extent of hypoperfusion. Timely reperfusion, maintenance of collateral circulation, and improvement in microcirculatory perfusion can all influence the subsequent fate of ischemic tissue [31]. Improvement in CBF-ASPECTS suggests a reduction in the extent of affected blood flow [32]. Improvement in CBV-ASPECTS may reflect blood volume compensation and restoration of perfusion reserve [33]. Improvement in ATT-ASPECTS indicates attenuation of delayed flow arrival [34]. The three scores focus on different aspects, and their combined observation can more completely reflect changes in perfusion status. If CBF and CBV improve only slightly while ATT remains prolonged, local tissue may still be in a state of inefficient perfusion [25]. In this situation, even if some indicators improve compared with baseline, the infarct core may continue to evolve. The overall increase in ICV observed in this study also indicates that perfusion improvement and infarct progression can coexist in the short term. This phenomenon is consistent with the complex features of lesion evolution after AIS. Correlation analysis showed a relatively clear relationship between short-term perfusion changes and 90-day mRS scores. Greater improvements in CBF-, CBV-, and ATT-related indicators were associated with lower 90-day mRS scores, suggesting better long-term functional outcome. When rATT decreased only slightly or ICV increased more markedly, functional outcomes tended to be worse. Among these indicators, ΔCBV-ASPECTS and ΔrCBV were more closely related to mRS score, suggesting that blood volume changes have useful reference value for prognosis assessment. Improved CBV may be related to preserved perfusion reserve in the ischemic region and may also reflect maintenance of local blood flow by collateral circulation. However, improvement in blood volume alone cannot fully indicate sufficient restoration of local perfusion, because timely flow arrival is also important. ATT-related indicators provide complementary information. A marked decrease in rATT indicates attenuation of delayed flow arrival and relatively improved local perfusion efficiency [34, 35]. If rATT improves only modestly, even when CBF or CBV recovers to some extent, the ischemic region may still have insufficient blood supply efficiency, and the infarct core may continue to expand [36, 37]. Therefore, combined observation of CBF, CBV, ATT, and ICV is more helpful than analysis of a single indicator for understanding the relationship between perfusion recovery and progression of tissue injury within 1 week after AIS onset. However, these findings should be interpreted as associations rather than evidence of a direct causal effect, because perfusion evolution might also be affected by recanalization status, collateral circulation, treatment response, and subsequent rehabilitation.

Correlation analysis mainly describes the directional relationship between perfusion changes and 90-day functional outcome. ROC analysis further examined whether these indicators could distinguish patients with unfavorable outcomes. The AUC values of individual dynamic ASL indicators were around 0.68, indicating moderate rather than high discriminative ability. Therefore, these single indicators should be used as supplementary imaging markers rather than standalone prediction tools. After integration of imaging and clinical factors, the discriminative performance improved. Model 1, Model 2, and Model 3 had AUCs of 0.786, 0.748, and 0.798, respectively, whereas the clinical-imag-

ing model (Model 4) showed the highest AUC of 0.846. This indicates that dynamic ASPECTS perfusion scores have added value, but their prognostic interpretation is more reliable when combined with age, onset-to-imaging time, and baseline neurological severity. The ASPECTS dynamic score model retained practical value as it reflected the spatial extent of perfusion abnormality on CBF, CBV, and ATT maps and was easier to interpret than purely numerical parameters. Subgroup analysis also suggested that the clinical-imaging model generally maintained discriminative performance across prespecified subgroups, although subgroup estimates should be interpreted cautiously because of smaller sample sizes. Overall, short-term changes in ASPECTS perfusion scores can not only quantify perfusion recovery but also help identify patients with insufficient perfusion recovery and a higher risk of poor 90-day functional outcome.

This study has several limitations. First, this was a single-center retrospective study, and included cases were required to have dual-time-point MRI data; therefore, sample selection may have been affected by examination completeness. The findings therefore require validation in prospective multicenter cohorts with more standardized follow-up imaging protocols. Second, acute-phase treatment modalities were not completely consistent among patients, and information such as vascular recanalization status, collateral circulation grading, and rehabilitation interventions was not fully included in the analysis. Although the clinical-imaging model adjusted for age, time from onset to first MRI, baseline NIHSS score, and dynamic ASPECTS perfusion changes, residual confounding from vascular and post-acute management factors cannot be excluded. Third, ASPECTS perfusion scoring is a semi-quantitative evaluation method, and threshold setting and reader experience may affect the scoring results [38]. The > 0.2 threshold was prespecified to reduce false-positive regional scoring caused by minor interhemispheric asymmetry or image noise, but this pragmatic cutoff still requires further validation. Nevertheless, this study compared dual-time-point perfusion changes within the same evaluation framework and combined the analysis with quantitative values and ICV, which can still reflect early perfusion evolution characteristics in AIS. Future multicenter prospective studies may further integrate vascular imaging, structural imaging, and clinical variables to validate the application value of dual-time-point multi-PLD ASL in AIS prognosis assessment.

Conclusion

Dual-time-point multi-PLD ASL can be used to observe dynamic perfusion changes from the early stage after onset to 1 week after onset in patients with AIS. Compared to single baseline imaging, short-term follow-up can further show the direction of perfusion recovery, changes in delayed flow arrival, and infarct core evolution. Changes in ASPECTS perfusion scores were associated with 90-day functional outcomes, and combined analysis of dynamic scores improved the discrimination of unfavorable outcomes. This method has good interpretability and may serve as an imaging supplement for early prognosis in patients with AIS.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Components of the clinical-imaging model

Subgroup	n	Unfavorable outcome, n (%)	AUC	95% CI	*P* value
Age < 65 years	197	68 (34.5)	0.812	0.748-0.876	< 0.001
Age ≥ 65 years	267	135 (50.6)	0.786	0.731-0.841	< 0.001
Baseline NIHSS ≤ 8	260	74 (28.5)	0.803	0.747-0.859	< 0.001
Baseline NIHSS > 8	204	129 (63.2)	0.775	0.708-0.842	< 0.001
Time from onset to first MRI ≤ 4.5 h	247	86 (34.8)	0.815	0.761-0.869	< 0.001
Time from onset to first MRI > 4.5 h	217	117 (53.9)	0.779	0.715-0.843	< 0.001

Note: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; ASL, arterial spin labeling; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; ATT, arterial transit time. The clinical-imaging model included age, time from onset to first MRI, baseline NIHSS score, ΔCBF-ASPECTS, ΔCBV-ASPECTS, and ΔATT-ASPECTS.

Supplementary Table 2. Inter-reader reliability of ASPECTS perfusion scoring

Value	Baseline ICC for total score (95% CI)	1-week ICC for total score (95% CI)	Baseline weighted kappa (95% CI)	1-week weighted kappa (95% CI)
CBF-ASPECTS	0.760 (0.719-0.796)	0.903 (0.885-0.919)	0.839 (0.807-0.870)	0.846 (0.815-0.876)
CBV-ASPECTS	0.753 (0.716-0.793)	0.887 (0.866-0.905)	0.818 (0.784-0.851)	0.826 (0.793-0.858)
ATT-ASPECTS	0.710 (0.662-0.752)	0.876 (0.853-0.895)	0.801 (0.765-0.835)	0.810 (0.775-0.843)

Note: ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; ATT, arterial transit time; ICC, intraclass correlation coefficient; CI, confidence interval. ICCs were used to assess inter-reader agreement for total ASPECTS perfusion scores, and weighted kappa values were used to assess agreement for regional abnormality classification.